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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/566,088	01/26/2006	Michael J. Caulfield	21468YP	5491

210 7590 01/08/2009

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EXAMINER	
DEVI, SARVAMANGALA J N	
ART UNIT	PAPER NUMBER
1645	
MAIL DATE	DELIVERY MODE
01/08/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/566,088	CAULFIELD ET AL.	
	Examiner	Art Unit	
	S. Devi, Ph.D.	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *091008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13* is/are pending in the application.

4a) Of the above claim(s) *9-13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *012606* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Preliminary Amendments

1) Acknowledgment is made of Applicant's preliminary amendments filed 05/15/08 and 09/10/08.

Election

2) Acknowledgment is made of Applicant's election filed 05/15/08 in response to the lack of unity mailed 03/13/08. Applicants have elected, with traverse, invention I, and the OMPC carrier protein species and the *H. influenzae* additional antigen species. Applicants' traversal is on the grounds that the Prodhomme abstract merely states that poly-D-gamma glutamic acid is an unusual gamma-linked polypeptide of high molecular weight (150-200 kDa), but does not teach that the polypeptide over 100 kDa was linked to an antibody. Applicants state that the abstract is silent as to the size of the polypeptide used in the conjugate. Applicants submit that the claims of inventions II, III and IV are linked by a unifying feature, the composition of the claims of invention I, and that there should be no greater burden to search and examine the non-elected claims and the claims of invention I. With regard to the species election requirement, Applicants contend that the recited carrier proteins are well known in the art as antigenic immunostimulatory proteins that are suitable for use as carrier proteins. Applicants assert that they may all be grouped and examined together as proteins often useful in stimulating immune responses against epitopes attached to them. Applicants submit similar arguments on the species election set forth for the additional antigen species and argue that these antigens do share common features.

Applicants' arguments have been carefully considered, but are not persuasive. As is clear form the art rejections set forth below, the conjugate of claim 1 comprising poly-D-gamma glutamic acid of over 100 kDa covalently linked to an immunogenic carrier protein was already disclosed in the art at the time of the invention. See the art rejections set forth below. Clearly, the product of claim 1 does not define over the prior art. As set forth previously, although the product of invention I, and the method of using the product of invention II and the method of making the product of invention III, is a permitted combination under PCT Rule 13.2, in the instant case, since the product is already disclosed in the art, the special technical feature is <u>not</u> a unifying feature. Technically, the absence of special technical feature permits the separation of the method of using

or making the product from the product itself. The method of invention IV lacks significant common method steps and reagents used with the methods of inventions II and III. Therefore, the lack of unity of inventions set forth in the instant application is proper and is hereby made FIANL. However, since Applicants have elected the product claims of invention I, inventions drawn to the method of using and the method making the product would be kept pending pursuant to the rejoinder provisions of M.P.E.P 821.04 and would be considered for rejoinder if and when the product claims are found to be allowable. With regard to Applicants' arguments on the species election requirement, it should be noted that the species are deemed to lack unity because they are not so linked as to form a single general inventive concept under PCT Rule 13.1. The various carrier protein species and the additional antigen species do not share a significant common structure; instead have mutually exclusive structural characteristics. Additionally, because of their divergent structure, a structure search for one would not necessarily identify all relevant prior art references on the other. Clearly, there is a serious search burden. Therefore, the species election requirement set forth in this application is proper and is hereby maintained.

However, Applicants should note that the examination has been extended to the second carrier protein species, recombinant Protective Antigen.

Status of Claims

3) Claims 1-13 are pending.

Claims 10-13 are withdrawn have been withdrawn from consideration as not being directed to the elected invention. See 37 C.F.R 1.142(b) and M.P.E.P § 821.03.

Claims 1-9 are under examination. A First Action on the Merits is issued on these claims.

Priority

4) The instant application is a national stage 371 application of PCT/US04/25033, filed 07/30/2004, which claims priority to the provisional application 60/491,478, filed on 07/30/2003.

Objection(s) to Specification

5) The instant specification is objected to for the following reason(s):

The use of trademarks in the instant specification has been noted in this application. For example, see page 27 for 'Tween 20'. All trademark recitations should be capitalized wherever they appear and be accompanied by the generic terminology. Each letter of the trademark must be

capitalized. See M.P.E.P 608.01(V) and Appendix l. Although the use of trademarks is permissible in patent applications, the propriety nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks. It is suggested that Applicants examine the whole specification to make similar corrections to the trademarks, wherever such recitations appear.

Rejection(s) under 35 U.S.C. § 112, Second Paragraph

6) The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude one or more claims particularly pointing out and distinctly claiming the subject matter which the Applicant regards as his/her invention.

7) Claims 5, 6, 7 and 9 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

(a) Claim 5 is indefinite and appears to be redundant in the limitation: 'Virus Virus' (see line 5).

(b) Claim 5 is incorrect in the limitation '*meningitides*' (see line 3), which is inconsistent with the limitation '*meningitidis*' recited in claim 6.

(c) Claim 7 lacks proper antecedent basis in the limitation: 'a conjugate of any of claims …'. Claim 7 depends from one of claims 1-6, which already include the recitation of a conjugate. It is suggested that Applicants provide proper antecedent basis to the above-identified limitation by replacing it with the limitation --the conjugate of any of claims …--.

(d) Claim 9 lacks proper antecedent basis in the limitation: 'A vaccine according to any of claims …'. Claim 9 depends from one of claims 7 and 8, which already include the recitation of a vaccine. It is suggested that Applicants provide proper antecedent basis to the above-identified limitation by replacing it with the limitation --The vaccine according to any of claims …--.

(e) Claim 9 is indefinite in the limitation: 'derived' (see line 3), because it is unclear what is encompassed in this limitation. Does 'derived' mean isolated, purified, separated, extracted, recombinantly expressed, surface exposed, or structurally modified or altered?

(f) Claim 9 is incorrect in the spelling of the limitation: Haemophilus 'influeza' and *Streptococcus* '*pneumonia*'.

(g) Claims 6, 7 and 9, which depend directly or indirectly from claim 5, are also rejected as being indefinite because of the indefiniteness identified above in the base claim.

Rejection(s) under 35 U.S.C. § 102

8) The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> **(a)** the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

9) Claims 1-3 and 5 are rejected under 35 U.S.C § 102(a) as being anticipated by Schneerson *et al.* (*PNAS* 100: 8945-8950, 22 July 2003) as evidenced by Prodhomme *et al.* (*Bioconjugate Chem.* 14: 1148-1155, 2003).

The limitation 'about .... kDa' in the claims is interpreted in this rejection as being equivalent to $\pm$ 30 kDa.

Schneerson *et al.* taught a conjugate comprising an isolated, native poly-D-gamma glutamic acid from *B. anthracis* covalently linked to an immunogenic carrier protein such as recombinant *Pseudomonas aeruginosa* exotoxin A, or recombinant *B. anthracis* protective antigen using 1-ethyl-3-(30dimethylaminopropyl)carbodiimide.HCl (EDC or EDAC) cross-liker. A vaccine comprising the conjugate and PBS (i.e., pharmaceutically acceptable excipient) is taught. The conjugate elicited anti-poly-D-gamma glutamic acid IgG antibodies in mice. See abstract, Table 1, left column on page 8947, and page 8948. That the prior art native poly-D-gamma glutamic acid has an intrinsic molecular weight of above about 100 kDa is inherent from the teachings of Schneerson *et al.* in light of what is well known in the art. Prodhomme *et al.* teach that a gamma-linked polypeptide of D-glutamic acid of molecular mass 100-300 kDa is found in several strains of *Bacillus* including *Bacillus anthracis.* See first full paragraph under 'Introduction' on page 1148 of Prodhomme *et al.*

Claims 1-3 and 5 are anticipated by Schneerson *et al.* The reference of Prodhomme *et al.* is **not** used as a secondary reference in combination with Schneerson *et al.*, but rather is used to show that every element of the claimed subject matter is disclosed by Schneerson *et al.* See *In re Samour* 197 USPQ 1 (CCPA 1978).

10) Claims 1-3 are rejected under 35 U.S.C § 102(b) as being anticipated by Goodman *et al.*

(*Biochemistry* 7: 706-710, 1968) as evidenced by Candela *et al.* (*Mol. Microbiol.* 57: 717-726, 2005) and Prodhomme *et al.* (*Bioconjugate Chem.* 14: 1148-1155, 2003).

The limitation 'about .... kDa' in the claims is interpreted in this rejection as being equivalent to $\pm$ 30 kDa. It is noted that the poly-gamma-D-glutamic acid and the immunogenic carrier protein recited in claims 1-3 are not required to be isolated and/or purified.

Goodman *et al.* taught an immunizing composition comprising heated suspensions of *Bacillus anthracis* comprising a poly-gamma-D-glutamic acid capsule. The composition raised antisera against the poly-gamma-D-glutamic acid capsule. See abstract and the first paragraph under 'Materials and Methods'. That the capsule in the prior art heated encapsulated *Bacillus anthracis* intrinsically comprises poly gamma-D-glutamic acid of molecular weight of above 100 kDa and is being naturally linked covalently to a *B. anthracis* surface protein (i.e., immunogenic carrier protein) directly or indirectly is inherent from the teachings of Goodman *et al.* in light of what is known in the art. For example, Candela *et al.* teach that poly gamma-D-glutamic acid is covalently linked to other protein-containing antigens on encapsulated *Bacillus anthracis.* See first paragraph under 'Results' and 'Summary'. Similarly, Prodhomme *et al.* teach that a gamma-linked polypeptide of D-glutamic acid of molecular mass 100-300 kDa is found in several strains of *Bacillus* including *Bacillus anthracis.* See first full paragraph under 'Introduction' on page 1148 of Prodhomme *et al.*

Claims 1-3 are anticipated by Goodman *et al.* The reference of Prodhomme *et al.* or Candela *et al.* is **not** used as a secondary reference in combination with Goodman *et al.*, but rather is used to show that every element of the claimed subject matter is disclosed by Goodman *et al.* See *In re Samour* 197 USPQ 1 (CCPA 1978).

Rejection(s) under 35 U.S.C. § 103

11) The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> **(a)** A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 148 USPQ 459, that are applied for establishing a background for determining obviousness under 35 U.S.C. § 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or unobviousness.

12) Claim 4 is rejected under 35 U.S.C § 103(a) as being unpatentable over Schneerson *et al.* (*PNAS* 100: 8945-8950, 22 July 2003) as applied to claims 1-3 above and further in view of Salceda *et al.* (US 6,855,517).

The reference of Salceda *et al.* is applied in this rejection because it qualifies as prior art under subsection (e) of 35 U.S.C § 102 and accordingly is not disqualified under U.S.C 103(a).

The teachings of Schneerson *et al.* are explained above, which do not disclose the use of N-(epsilon-maleimidocaproic acid)hydrazide (EMCH) linker.

However, the use of EMCH as a common heterobifunctional cross-linker alternative was routine in the production of conjugates. For example, Salceda *et al.* taught that polypeptides can be conjugated to other proteins using a common bifunctional linking reagent or cross-linker alternative to EDC such as EMCH. See last full paragraph in column 47.

It would have been *prima facie* obvious for one of ordinary skill in the art at the time the invention was made to replace the EDC or EDAC linker in Schneerson's conjugate with Salceda's alternative linker EMCH to produce the instant invention with a reasonable expectation of success. Substitution of one art-known linker with another alternative art-known linker is well within the realm of routine experimentation, would have been obvious to a skilled artisan and would have brought about similar predictable result or effect.

Claim 4 is *prima facie* obvious over the prior art of record.

13) Claim 6 is rejected under 35 U.S.C § 103(a) as being unpatentable over Schneerson *et al.* (*PNAS* 100: 8945-8950, 22 July 2003) as modified by Salceda *et al.* (US 6,855,517) as applied to claim 4 above and further in view of Perez-Melgosa *et al.* (*Eur. J. Immunol.* 31: 2373-2381, 2001).

The teachings of Schneerson *et al.* as modified by Salceda *et al.* is are explained above, which do not disclose the use of the outer membrane protein complex of *Neisseria meningitidis* as the carrier protein.

However, the advantageous use of a *N. meningitidis* outer membrane protein as a carrier protein in the production of a conjugate was conventional and well known in the art of conjugate vaccines. For instance, Perez-Melgosa *et al.* identified *N. meningitidis* OMPC to be unique and superior compared to other carrier proteins in that it serves both as a protein carrier and also as an adjuvant. See 'Abstract' and 'Discussion'.

It would have been *prima facie* obvious for one of ordinary skill in the art at the time the invention was made to replace the *Pseudomonas aeruginosa* exotoxin A carrier protein in Schneerson's conjugate with Perez-Melgosa's advantageous carrier protein, the outer membrane protein complex of *N. meningitidis*, to produce the instant invention with a reasonable expectation of success. One of ordinary skill in the art would have been motivated to produce the instant invention for the expected benefit of providing an art-known carrier protein which advantageously serves not only as an effective carrier protein but also as an adjuvant as taught by Perez-Melgosa *et al.*

Claim 6 is *prima facie* obvious over the prior art of record.

14) Claim 7 is rejected under 35 U.S.C § 103(a) as being unpatentable over Schneerson *et al.* (*PNAS* 100: 8945-8950, 22 July 2003) as applied to claims 1-3 above.

The teachings of Schneerson *et al.* are explained above, which do not disclose the use of an adjuvant in their conjugate vaccine.

However, adding an art-known adjuvant to a prior art conjugate vaccine was routine and conventionally practiced in the art for the purpose of enhancing the immunogenicity of the conjugate. Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to add an art-known adjuvant such as aluminum hydroxide adjuvant to the prior art conjugate vaccine to produce the instant invention with a reasonable expectation of success, since it is routine and conventional in the art of conjugate vaccines to add an art-known adjuvant thereto for the purpose of improving the immunogenicity of the conjugate.

Claim 7 is *prima facie* obvious over the prior art of record.

15) Claim 9 is rejected under 35 U.S.C § 103(a) as being unpatentable over Schneerson *et al.* (*PNAS* 100: 8945-8950, 22 July 2003) as applied to claim 7 above and further in view of O'Hagan (US 20050118275).

The reference of O'Hagan is applied in this rejection because it qualifies as prior art under subsection (e) of 35 U.S.C § 102 and accordingly is not disqualified under U.S.C 103(a).

The teachings of Schneerson *et al.* as applied to claim 7 are explained above, which do not disclose that their conjugate vaccine further comprises an antigen from *Haemophilus influenzae*.

However, the concept of mixing an antigen of *Haemophilus influenzae* with that of anthrax was known in the art at the time of the invention. For example, O'Hagan taught combining an antigen of *Haemophilus influenzae* with an antigen of anthrax. See section [0098].

Given the art-known practice of combining an antigen of *Haemophilus influenzae* with an antigen of anthrax as taught by O'Hagan, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to add an art-known antigen of *Haemophilus influenzae* to the conjugate vaccine of Schneerson *et al.* as applied to claim 7 to produce the instant invention. One of ordinary skill in the art would have been motivated to produce the instant invention for the expected benefit of advantageously providing immunity to more than one bacterial pathogen with a single vaccine composition.

Claim 9 is *prima facie* obvious over the prior art of record.

16) Claim 8 is rejected under 35 U.S.C § 103(a) as being unpatentable over Senyk *et al.* (*Immunochemistry* 9: 97-110, 1972) in view of Salceda *et al.* (US 6,855,517) and Perez-Melgosa *et al.* (*Eur. J. Immunol.* 31: 2373-2381, 2001).

Senyk *et al.* taught an immunizing composition (i.e., vaccine) comprising an isolated poly-gamma-D-glutamic acid conjugated to glucagon polypeptide, water and CFA adjuvant. See abstract; pages 97 and 107, and paragraph bridging pages 98 and 99.

Senyk *et al.* do not teach the use of the outer membrane protein complex of *Neisseria meningitidis* as the carrier protein and N-(epsilon-maleimidocaproic acid)hydrazide (EMCH) linker.

However, the use of EMCH as a common heterobifunctional cross-linker was routine in the production of conjugates. For example, Salceda *et al*. taught that polypeptides can be conjugated to other proteins using a common bifunctional linking reagent or cross-linker alternative to EDC such as EMCH. See last full paragraph in column 47.

Likewise, the use of a *N. meningitidis* outer membrane protein as a carrier protein in the production of a conjugate was conventional and well known in the art of conjugate vaccines. For instance, Perez-Melgosa *et al*. identified *N. meningitidis* OMPC to be unique and superior compared to other carrier proteins in that it serves both as a protein carrier and also as an adjuvant. See 'Abstract' and 'Discussion'.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to replace the EDC or EDAC linker in Schneerson's conjugate with Salceda's alternative linker EMCH and replace the *Pseudomonas aeruginosa* exotoxin A carrier protein in Schneerson's conjugate with Perez-Melgosa's advantageous carrier protein, the outer membrane protein complex of *N. meningitidis*, to produce the instant invention with a reasonable expectation of success. Substitution of one art-known linker with another alternative art-known linker is well within the realm of routine experimentation, would have been obvious to a skilled artisan and would have brought about similar predictable result or effect. One of ordinary skill in the art would have been motivated to produce the instant invention for the expected benefit of providing an art-known carrier protein which advantageously serves not only as an effective carrier protein but also as an adjuvant as taught by Perez-Melgosa *et al*.

Claim 8 is *prima facie* obvious over the prior art of record.

Objection(s) to Claims

17) Claim 9 is objected to for the following reasons:

(a) Claim 9 is objected to for the non-italicized and incorrect limitation: 'Haemophilus influenza'. It is suggested that Applicants replace the limitation with --*Haemophilus influenzae*--.

(b) Claim 9 is objected to for the incorrect limitation: *Streptococcus 'pneumonia'*. Pneumonia represents a clinical condition, not a part of the name of the streptococcal species.

Relevant Prior Art

18) The prior art made of record and not currently relied upon in any of the rejections is considered pertinent to Applicants' disclosure:

- Blanchard *et al.* (*FASEB J.* 2: A1257, abstract 5590, 1988) taught an immunogenic composition comprising *Bacillus* polyglutamic acid covalently bound to anti-tetanus toxoid antibodies for immunization of guinea pigs. See entire abstract.

Remarks

19) Claims 1-9 stand rejected.

20) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted to the Office's Central Rightfax number 571-273-8300 via the PTO Fax Center, which receives transmissions 24 hours a day and 7 days a week.

21) Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAG or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.Mov. Should you have questions on access to the Private PAA system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (in USA or CANADA) or 571-272-1000.

22) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (571) 272-0854. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Robert Mondesi, can be reached on (571) 272-0956.

/S. Devi/
Primary Examiner, AU 1645

January, 2009